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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,082	02/28/2002	Wolfgang Dietmaier	18668-US1	3192

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EXAMINER	
CHUNDURU, SURYAPRABHA	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,082	DIETMAIER ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on December 6, 2005 has been entered and acknowledged.

Status of the Application

2. Claims 1, 3-17 are pending. Claims 1 and 9 are currently amended. Claim 2 is previously cancelled. Applicants' response to the office action is fully considered. All arguments have been fully considered and thoroughly reviewed, but are deemed persuasive in part for the reasons that follow. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is made FINAL.

3. The following rejection is made in the previous office action:

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eggeling et al. (Hum Genet., Vol. 99, pages 266-270, 1997) in view of Biochemicals Catalog, (Biochemicals Catalog, Boehringer Mannheim, page 153, 1997).

Eggeling et al. teach a method of claims 1, 9, for the amplification of nucleic acid fragments from a sample, wherein said nucleic acid fragments are between 100 and 1000 base pairs (see page 267, col. 2, line 4-7 under Results section) said method comprises first (primer extension pre amplification) and second (specific amplification), wherein said first amplification is carried out using completely randomized primers (see page 267, column 1, paragraph 3 of materials and methods section) and said second amplification reaction is carried out using specific primers (see page 267, column 1, paragraph 5 under Materials and methods section) and wherein in said first amplification reaction, the temperature at which primer extension is carried out is increases in at least some of the successive amplification cycles (see page 267, col. 1, paragraph 3, of materials and methods section).

With regard to claims 6, 14, Eggeling et al. teach that said sample comprises cells (blood cells) (see page 267, column 1, paragraph 1 under materials and methods);

With regard to claims 7-8, 15-16, Eggeling et al. treating sample of cells with proteinase K (see page 267, column 1, paragraph 2 under materials and methods section);

However, Eggeling et al. did not teach use of a mixture of at least two thermostable DNA polymerases, said mixture comprising at least one DNA polymerase without 3'-5' exonuclease activity and a DNA polymerase with 3'-5' exonuclease activity and said sample comprising a pool of cDNAs.

With regard to claims 1, 3-17, Biochemicals Catalog teaches use of a mixture of at least two thermostable DNA polymerases (Expand™ high fidelity polymerases) for amplification of nucleic acid fragments up to 6 kb which includes nucleic acid fragments between 1 base and 6kb in length) (see page 153, col. 1, line 10-16 of paragraph 2, col. 2, Fig. Indicating various PCR fragments ranging from 145 bp to 4kb in length) and said mixture of DNA polymerases comprises a DNA polymerase without 3'-5' exonuclease activity (Taq DNA polymerase) and a DNA polymerase with 3'-5' exonuclease activity (Pwo DNA polymerase) (see page 153, col. 1, line 5-8, of paragraph 1, line 10-16 of paragraph 2, as claimed in claims 5, and 13).

With regard to claims 4, 12, Biochemical Catalog teaches amplification of cDNA population using said mixture of DNA polymerases (see page 153, col. 1, line 4-9 of paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to amplify nucleic acid fragments of Eggeling et al. in a manner taught by Biochemicals Catalog using the mixture of DNA polymerases (Expand™ high fidelity polymerases) having high fidelity to achieve expected benefit of developing an enhanced sensitive method of amplification because Biochemicals Catalog taught that the use of the combination of DNA polymerases reduces secondary structures and provides lower error rate and provides high fidelity PCR system in amplifying entire population of transcripts without the need to construct cDNA libraries (see page 153, col. 1, line 10-16 of paragraph 2, line 4-9 of paragraph 3). An ordinary practitioner would have been motivated to combine the method of amplification of a nucleic acid as taught by Eggeling et al. with the step of adding a mixture of at least two DNA polymerases in order to achieve low error rate during primer extension. The

ordinary artisan would have a reasonable expectation of success that inclusion of the mixture of DNA polymerases would result in an increase in fidelity as compared to the use of a single DNA polymerase and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Response to Arguments:

5. Applicants' arguments and amendment filed on December 06, 2005 have been fully considered and found persuasive in part.

6. With regard to the objection made in the previous office action to the foreign priority document, Applicants' submission of an English translation to the priority document is fully considered and found persuasive. The objection is withdrawn herein in view of the submission of an English translation to the priority document.

7. Applicant's arguments filed on December 06, 2005, with respect to the rejection under 102(a) as being anticipated by Dietmaier et al. have been fully considered and are persuasive. The rejection of claims 1, 3, 5-11, 13-17 has been withdrawn in view of the submission of an English translation to the foreign priority document.

8. The Declaration under 37 CFR 1.132 filed on December 06, 2005 is insufficient to overcome the rejection of claims 1, 3-17 based upon obviousness as set forth in the last Office action. The Declaration by Dr. Gregor Sanger is fully considered and found unpersuasive. The Declaration states the combination of references on record does not provide any motivation to combine the teachings of Eggerling et al. with the teachings of Biochemicals Catalog to expect amplification of nucleic acid fragments between 100 to 550 bases. If the claim were drawn to amplify specific small templates (within 100-550 bases) with the use of a mixture of two DNA polymerases, at

least one of which having high fidelity or 3'-5'-exonuclease activity, the Declaration does not address or show any data or results to support the nonobviousness. In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

9. Applicant's arguments filed on December 06, 2005, with regard to the rejection of claims 1, 3-17 under 35 USC 103(a) have been fully considered but they are not persuasive. Applicants' argue that there is no motivation to combine the teachings of Eggeling and the Biochemicals Catalog and asserts that one skilled in the art would not have been motivated to use Expand™ high fidelity enzyme blend as described in the Biochemicals Catalog with the Eggeling method and argue that the enzyme blend is used for amplification of nucleic acid fragments up to 6kb that results in reduced error rate or secondary structures and increase in fidelity of amplification. Applicants further argue that the Examiner failed to demonstrate that the Taq polymerase (which lacks 3'-5' exonuclease activity) of Eggeling method would motivate one skilled in the art to use the enzyme with high fidelity (3'-5' exonuclease activity). In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection which states that one of ordinary skill in the art at the time the invention was made would have motivated to amplify nucleic acid fragments of Eggeling et al. in a manner taught by

Biochemicals Catalog using the mixture of DNA polymerases (Expand^{TM} high fidelity polymerases) having high fidelity to achieve expected benefit of developing an enhanced sensitive method of amplification because Biochemicals Catalog taught that the use of the combination of DNA polymerases reduces secondary structures and provides lower error rate and provides high fidelity PCR system in amplifying entire population of transcripts without the need to construct cDNA libraries (see page 153, col. 1, line 10-16 of paragraph 2, line 4-9 of paragraph 3). An ordinary practitioner would have been motivated to combine the method of amplification of a nucleic acid as taught by Eggeling et al. with the step of adding a mixture of at least two DNA polymerases in order to achieve low error rate during primer extension. The ordinary artisan would have a reasonable expectation of success that inclusion of the mixture of DNA polymerases would result in an increase in fidelity as compared to the use of a single DNA polymerase and such modification of the method would be obvious over the cited prior art in the absence of secondary considerations.

Applicants also argue that the Declaration by Dr. Gregor Sanger supports that the references on record are not combinable because the enzyme blend of Biochemicals Catalog is intended to amplify long templates (>1000bp) and argue that Dr. Sanger explains that amplification of PCR fragments of about 550 bp or smaller does not require the use of high Fidelity enzymes. Applicants further argue that the Declartion explains that Eggeling et al. uses Taq DNA polymerase for first and second round of amplifications and the second round of amplification is directed to amplification of microsatellite loci wtihout mentioning the size, and Applicants assert that such amplification results in products of about 106/112 bp in size, and

argue microsatellite loci are typically below 100bp and argue that Dr. Gregor Sanger has explained why there is no motivation to combine the references on record.

The Declartion and the arguments are fully considered and found unpersuasive. First the Biochemicals Catalog teaches that the enzyme blend is used to amplify nucleic acid fragments upto 6kb. Thus it includes any fragment between 1 bp to 6Kb. Further the catalog demonstrates the amplification of small fragments as well as long nucleic acid fragments (see page 153, col. 2, Fig. Indicating various PCR fragments ranging from 145 bp to 4kb in length). Thus the arguments that the use of Expand high fidelity enzyme blend for amplification of small fragments is not required are unpersuasive. Further, Examiner notes that if it is not necessary to use a mixture of DNA polymerases at least one of which has a 3'-5' exonuclease, the invention drawn to amplify small templates should not have used said enzyme mix as claimed. Applicants further argue that the instant claims 1 and 9 have been amended to recite the limitation of "fragments between 100 and 550 base pairs in length" and assert that the in such "small template" amplification fidelity was not of a concern to those skilled in the art and there was no motivation to modify Eggeling et al. method with the use of the enzyme blend taught by Biochemicals catalog because such combination would confer no benefit in the practice of the method of Eggeling et al. and therefore the prior art of the record would have tended to teach away from such substitution. Applicants' arguments are fully considered and found unpersuasive. As noted in MPEP 2145 notes A prior art reference that "teaches away" from the claimed invention is a significant factor to be considered in determining obviousness; however, "the nature of the teaching is highly relevant and must be weighed in substance. A known or obvious composition does not become patentable simply because it has been described as somewhat

inferior to some other product for the same use." In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)." a teacing away is is teaching in a highly relevant factor in determining obviousness. In the instant context, the use of a mixture of DNA polymerase at least one of which having a proof reading activity (3'-5' exonuclease activity) , which is highly relevant to the instnat invention wherein the use of said enzyme blend would reduce the error rate and provide a specific accurate amplification product.

Further, as discussed above the use of the enzyme blend taught by Biochemicals is not confined to amplify long templates and the method of Eggeling et al. uses random primers in the first round of amplification which generates fragments of varied lengths and it is obvious to combine such method with the use of high fidelity DNA polymerase taught by Biochemicals catalog to amplify specific nucleic acid fragments to achieve accurate amplification products that reduces errors in primer extension and to reduce any secondary structures. Therefore the use of an enzyme blend is not confined to a length of a template rather it is used to achieve an accurate amplification product with reduced error rate. Therefore the rejection is maintained herein.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Prabha Chunduru

Suryaprabha Chunduru 2/21/06
Patent Examiner
Art Unit 1637